(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 273 579 A2**

(1)

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **87310331.1**

(51) Int. Cl.⁴: **A61K 7/28** , A61K 37/24

(22) Date of filing: **23.11.87**

A request for correction of the originally filed description has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

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(30) Priority: **22.11.86 JP 279497/86**

(43) Date of publication of application:
06.07.88 Bulletin 88/27

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

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(54) A composition for periodontal use.

(57) Superoxide dismutase (e.g. 1×10^{4} to 1.0 wt percent), optionally along with catalase (e.g. 1×10^{4} to 1.0 wt percent) and/or one or more amino acids such as taurine (e.g. 0.05 to 5.0 wt percent) is used in compositions such as solids (tablets, dentifrice) ointments, or liquids for application to the gingivae to treat or prevent inception of alveolar pyorrhea.

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A COMPOSITION FOR PERIODONTAL USE

This invention relates to a composition for periodontal use. More especially, it relates to a composition for periodontal use which can be applied for treatment and/or prevention of periodontal diseases, in particular alveolar pyorrhea.

The morbidity rate of periodontal disease is markedly increasing. According to dentists in general practice three in ten persons in the thirties already have the initial symptoms of alveolar pyorrhea. The initial symptoms begin with damage of keratine layer. Gums begin to bleed in biting (say) an apple or on tooth brushing, and bad breath is often a consequence. Healthy gingivae are usually pink-colored and stiff, whereas, in the initial stage of periodontal lesions, the gingivae deepen in color at the edges to a red coloration, sometimes dark red, increase in thickness with swelling, and bleed even on light touch. The exact mechnism of the progress of periodontal diseases is not known. It is assumed that proliferation of anaerobic bacteria occurs in the lesions and gives rise to alveolar pyorrhea. Alveolar pyorrhea then proceeds followed by pocket formation, loosening of teeth and finally loss of teeth. The loss rate of teeth due to such periodontal disease increases with age to exceed the loss rate by cariosity in the forties, and reach a maximum in the sixties. In other words, periodontal disease jeopardizes the tooth life, whereby it is a threat to general health in older people.

Current dietary habits of eating high proportions of cooked or processed food rather than raw or natural food, may affect, to a considerable degree, the morbidity rate of periodontal diseases. Prevention of periodontal disease has needed regular cleaning of dental plaque and periodontal elimination of dental calculus, together with stimulation and massage of gingivae. However, regular and strict execution of these techniques is not always easy in daily life.

Many other methods have been reported for prevention of periodontal diseases, for example, application of various kinds of antibacterial agents or of enzymes that decompose glucagon (which may be responsible for dental plaque formation) or use of electrolytes as an astringent for gingivae. However, none of these have been thoroughly successful. Although these expedients have also been tried for treatment of alveolar pyorrhea, they are only an auxiliary therapy to surgical operation. No drug effective against alveolar pyorrhea, has yet been found. For effective treatment of alveolar pyorrhea, surgical operations (such as scaling, pocket curettage, gingivectomy, flap operation or others) are currently necessary.

Nowadays, especially since a higher proportion of people survive to old age the development of a simple and non-surgical method for prevention and/or treatment of periodontal diseases, in particular alveolar pyorrhea is of major interest. The present invention sets out to provide an effective and simple method for prevention and/or treatment of periodontal diseases, in particular alveolar pyorrhea. The present invention further sets out to achieve prolongation of average tooth life.

I have found that, by applying superoxide dismutase to the lesion, periodontal diseases, in particular alveolar pyorrhea can be alleviated or in some instance completely cured and moreover that by applying superoxide dismutase to gingivae, periodontal diseases can be prevented.

Thus, the present invention consists in a composition for periodontal use, which is characterised by containing superioxide dismutase as an active ingredient. The present invention in another aspect consists in a method for treating or preventing periodontal diseases, in particular alveolar pyorrhea, which is characterised by using superoxide dismutase or compositions, e.g. as described below, containing such.

Yet another aspect of the invention consists in the use of superoxide dismutase in the preparation of a composition for periodontal application.

The process for manufacturing superoxide dismutase is known from earlier literature and patents. For example, it can be manufactured by extraction and purification from various organs such as liver, erythrocytes and placenta of animals (bovine or human) or from bacteria such as Escherichia coli, and genetically manipulated cells.

Superoxide dismutase has been proposed as a therapeutic agent for osteoarthritis, rheumatoid arthritis and irradiation injury which are all possibly related to tissue damage due to superoxide. However, its half life in blood is as short as 6 minutes. and success in safe and effective treatment of human diseases has not been reported yet. There are no reports which suggest the application of superoxide dismutase to alveolar pyorrhea as in the present invention.

The superoxide dismutase to be employed for the purpose of the present invention may be any type of superoxide dismutase, and the invention is not limited by its source or manufacturing process. Unless the activity of superoxide dismutase is greatly impaired, any active portion of the enzyme, or a modified superoxide dismutase, can be used in the present invention and be included in the term 'suproxide dismutase' used in this specification. However, bovine or human superoxide dismutases are preferable.

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The content of superoxide dismutase in the present composition depends on the form selected. Since superoxide dismutase displays the effect of interest to the present invention even in small amounts, the content in the made-up composition will generally be in the range between about 1×10^{-4} weight percent and about 1 weight percent based on the total weight of the composition (i.e. between about 3×10^{-8} and about 3×10^{-4} molar percent). When it is used for prevention, a lower concentration of superoxide dismutase can be employed.

When superoxide dismutase is applied to gingivae, it may be assumed to resolve superoxide to hydrogen peroxide. The latter may then react with chlorine ion naturally present to form hydrochlorite. Therefore, it is advantageous to add catalase and/or one or more amino acids or derivatives thereof in the present composition in order to remove hydrogen peroxide and hypochlorite, respectively. For this purpose, commercially available catalase can be generally added in the concentration range between about 1×10^{-4} and about 1 weight percent in the composition. Amino acids or derivatives thereof, preferably selected from taurine, glycine, aspartic acid, histidine, lysine and acyl glutamic acid (taurine is most preferable) can be present generally within the range from about 0.05 to about 5 weight percent of the total composition.

The present composition for periodontal use, containing superoxide dismutase as an active ingredient, can be produced in any conventional form capable of application to gingivae.

The effect of superoxide dismutase in treatment of periodontal diseases, in particular alveolar pyorrhea can for instance be manifested by injecting or infusing a solution into periodontal areas or pockets, or by flooding them in such solution. Thus, the composition of the present invention may be in a form of a solution for injection or infusion, e.g. such as a mouth wash. In order to keep superoxide dismutase in contact with gingivae for a sufficient time, the composition may alternatively be in the form of a tablet, (especially a tablet which on dissolution produces a liquid adhesive to gingivae), or a chewing-gum. It may alternatively be an oil-type or emulsion type ointment or gel formulation, which can be applied upon or rubbed into gingivae. A form especially suitable for prevention purposes is a conventional form of dentifrice such as a paste. Powder or semi-paste. For example, superoxide dismutase can be introduced into a conventional dentifrice.

Superoxide dismutase is stable against heat, has an optimum pH range of about 7 to 9 and a stable pH range of about 6 to 11. It is inactivated only in the presence of a strong acid or alkali, or a potent chelating agent. Thus, in manufacturing the present omposition, any non-toxic conventional base and any conventional method well-known in the art can be employed. Moreover, in the present composition. other conventional active ingredients or adjuvant ingredients such as various kinds of enzymes, fluorine compounds, antibiotics, vitamins and other can also be added.

The present composition for injection or infusion can be manufactured by dissolving superoxide dismutase and optionally methylcellulose, sorbitol, serum albumin, preservatives and a flavoring agent, and after sterilisation, filling the solution into ampoules or vials. It may be in a lyophilized form.

Mouth wash can be produced by a conventional method employing optionally boric acid, borax and aluminium potassium sulfate. Flavoring agents, sweetening agents or preservatives can be added.

Tablets can be produced by any conventional method, employing the superoxide dismutase with optional ingredients chosen from diluting agents, binding agents, flavoring agents, coloring agents, lubricants, preservatives, sweetening agents and others. Examples of the diluting agents are various kinds of cellulose ethers, acrylate polymers, starch, dextrin, milk sugar, sorbitol and calcium phosphate. Examples of binding agents are starch, dextrin, gelatin, tragacanth and others. Further addition of polyvinyl alcohol can confer adhesiveness on the tablet.

Chewing-gum can also be produced by any conventional method, e.g. employing a gum base as vinyl acetate polymer, and binding agents, diluting agents, flavoring agents, coloring agents, preservatives and sweetening agents can be added as described above in connection with tablets.

Ointment or gel formulations in accordance with the present invention can be produced employing a suitable base and additives depending on the properties and form desired. Examples of the bases are water, glycerol, 1,3-butanediol, proplylene glycol, polyethylene glycol, polypropylene glycol, ethanol, various kinds of cellulose ether, polyvinyl alcohol, carboxyvinyl alcohol, cetyl alcohol, vaseline and liquid paraffin. If necessary, tensides such as polyoxyethylene sorbitan fatty ester, polyoxyethylene fatter ester, polyoxyethylene alkyl ether and others can be combined in the preparation. Further, there may be added a flavoring agent, coloring agent, preservative and sweetening agent.

Dentifrices in accordance with the present invention can be produced employing a suitable base and additives depending on the properties and form desired. Examples of the bases suitable for preparing paste, powder or semi-paste, are calcium phosphate, calcium carbonate, aluminium hydroxide, insoluble metaphosphoric acid, calcium pyrophosphate, magnesium carbonate, silicic acid and salts thereof and pulverised polymer. In addition, wetting agents such as glycerol, sorbitol, propylene glycol, polyethylene

glycol and others, and binding agents such as bentonite, sodium carboxymethylcellulose, hydroxyvinyl polymer and tragacanth gum can be used. Futhermore, if necessary, tensides such as alkylsulfate, alklsulfonate, glycerol fatty acid ester, sorbitan fatty ester, flavoring agents, sweetening agents, coloring agents and preservatives can be added.

The present composition can be used at any stage of the periodontal disease for the purpose of treatment. The efficacies of the present composition and method are apparent from clinical studies using twenty patients with alveolar pyorrhea. After dental calculus was removed briefly with an ultrasonic scaler, a superoxide dismutase solution (Concentration : 0.5×10^{6} or 1.0×10^{6} M) was filled into the remaining dental pockets, which were then curetted slightly with a scaler. Next, the patients brushed their teeth and gingivae with a tooth-brush immersed in the above superoxide dismutase solution, and maintained for a while a pose which can keep the solution filled in the pockets. This therapy was repeated once a week for three weeks.

In this clinical study, all twenty cases showed improvement of alveolar pyorrhea. That is, the depth of pocket, as measured by a pocket probe, decreased from the average of 8.0 mm before treatment, to the average of 2.5 mm (range : 1 - 5 mm) after three times treatment (normal value : 1 - 2 mm). In most cases, violet or dark red colored gingivae were improved to pink-colored only one week after the first therapy. Subjective conditions such as pain and objective syndromes such as loss of teeth were also eliminated. No side effects were observed.

It is surprising that alveolar pyorrha a disease, an effective conservation therapy for which has not hitherto been known was improved within a relatively short period, using only extremely small amounts of superoxide dismutase.

For the purpose of prevention, the use of superoxide dismutase in the form of usual dentifrices is preferable.

The present invention will be further illustrated in detail in the following examples without limiting the scope of the invention as claimed.

Example 1 : Solution for infusion

Component	per 100 ml
Superoxide dismutase	0.003 g
Methylcellulose	3 g
Sorbitol	10 g
Purified water	to 100 ml

Methylcellulose is slowly added to purified water to give a homogeneous solution, to which is then added the rest of the components. After adjusting the total volume, the solution is filtered through a milipore filter for sterilisation, and filled into a suitable vial. A pale blue solution is obtained.

Example 2 : Solution for injection

A solution as described for infusion in Example 1 is made up and catalase (0.01 g/100 ml) and taurine (1 g/100 ml) is added.

Example 3 : Lyophilized preparation

Superoxide dismutase (0.01 g) is dissolved in 5, human serum albumin solution and the total volume is adjusted to 100 ml. Each 10 ml of the solution is filled into a 30 ml vial, and lyophilized. Prior to use, 10 ml of water is added to give a reproducible and infusible solution.

Example 4 : Tablet

Component	(per tablet)
Superoxide dismutase	0.001 mg
Microcrystalline cellulose	120 mg
Magnesium stearate	1.5 mg
Polyvinyl alcohol	30 mg
Pectin	9 mg
Hydrogenated oil	3 mg
Milk sugar	136.6 mg
Total	300.0 mg

The above components are mixed thoroughly and compressed to obtain a plain tablet. When dissolved in the mouth this tablet gives a liquid with adhesiveness to the gingivae, and can therefore release superoxide dismutase slowly.

Example 5 : Tablet

Tablets containing, in addition to the components as in the tablet of Example 4, catalase (0.01 mg/tablet) and taurine (10 mg/tablet), are prepared in the same manner as described in Example 4.

Example 6 : Oil-type ointment

Component	per 100 mg
A : Superoxide dismutase	0.003 g
Purified water	1.0 g
Propylene glycol	1.0 g
B : Polyvinyl alcohol	5.0 g
Liquid paraffin	40.0 g
White vaselin	ad to 100 g

The items of component B are combined and melted by heating to a temperature of 70 - 75°C on a water bath. After cooling of the melt to 45 - 50°C, the items of component A is added with stirring to produce a homogeneous oil type ointment.

Example 7 : Emulsion-type ointment

Components		per 100 g
A :	Superoxide dismutase	0.01 g
B :	Stearyl alcohol	5.0 g
	White vaseline	8.0 g
	Liquid paraffin	8.0 g
	Polyoxyethylene (20) sorbitan monostearate	4.0 g
	Sorbitan monostearate	2.0 g
	Glycerol fatty ester	4.0 g
	Butyl p-hydroxybenzoate	0.05 g
C :	Methyl p]hydroxybenzoate	0.1 g
	Citric acid	0.04 g
	Propylene gylcol	10.0 g
	Purified water	to 100 g

The items of component B are combined and melted by heating to a temperature of 70 - 75°C. The items of component C are then preheated to 70 - 75°C with stirring, and added to component B to obtain an emulsion. After stirring for 15 minutes, the emulsion is cooled to 50°C with water and the items of component A, dissolved in purified water, are added with stirring to produce a homogeneous emulsion-type ointment.

Example 9 : Aqueous gel

Component		
A :	Superoxide dismutase	0.003 g
	Taurine	1.0 g
B :	Carboxyvinyl polymer	1.0 g
C :	Sodium hydroxide	q.s.
D :	Glycerol	10.0 g
	Ethanol	3.0 g
	Purified water	ad to total 100 g

The mixture of items constituting D is slowly added to and dispersed homogeneously within component B. To this dispersion, the items of component A, dissolved in purified water, are added and homogeneously dissolved. The pH of the dispersion is adjusted to 6.5 with the sodium hydroxide (component C) to obtain an aqueous gel.

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Example 10 : Tooth paste

Component		per 100 g
A :	Superoxide dismutase	0.001 g
	Sodium lauryl sulfate	2.0 g
	Sodium lauroyl sarcosinate	0.2 g
	Calcium hydrogen phosphate	40.0 g
	Magnesium phosphate	0.5 g
	Silicic anhydride	2.0 g
B :	Glycerol	15.0 g
	Sorbitol	10.0 g
	Sodium lactate	2.0 g
	Carboxymethylcellurose	1.0 g
	Methyl p-phydroxybenzoate	0.05 g
	Ethyl p-hydroxybenzoate	0.05 g
	Perfume	q.s
	Purfied water	ad to total 100 g

The individual items of component B, except the perfume, are mixed into a homogeneous solution. This solution is combined with the items of component A successively under kneading. Finally the perfume is added. A homogeneous tooth paste is obtained.

Claims

1. A composition for periodontal use characterised in that it contains superoxide dismutase.
2. A composition according to Claim 1, characterised in that the superoxide dismutase is human superoxide dismutase.
3. A composition according to Claim 1, characterised in that the superoxide dismutase is bovine superoxide dismutase.
4. A composition according to any one of Claims 1 to 3, characterised in that the superoxide dismutase is present in an amount within the range from 1×10^{-4} weight percent to 1 weight percent based on the total weight of the composition.
5. A composition according to any one of Claims 1 to 4 characterised in that it further contains catalase.
6. A composition according to Claim 5, characterised in that the catalase is present in an amount within the range from 1×10^{-4} weight percent to 1 weight percent based on the total weight of the composition.
7. A composition according to any one of Claims 1 to 6, characterised in that it further contains one or more amino acids, or derivatives thereof.
8. A composition according to Claim 7, characterised in that the amino acid or derivative thereof is selected from taurine, glycine, aspartic acid, histidine, lysine or acyl glutamic acid.

9. A composition according to Claims 7 or 8. Wherein the amino acid or derivative thereof is present in an amount within the range from 0.05 weight percent to 5 weight percent based on the total weight of the composition.

10. A composition according to any one of the preceeding claims, characterised in that the composition is prsented in the form of solution, a solid composition, an ointment or gel or a dentifrice.

11. A composition according to any one of Claims 1 to 9 characterised in that the composition is presented in the form of an injectible solution, an infusible solution, a mouthwash or oral lotion, a tablet, a chewable tablet forming a liquid adherent to gingivae, a chewing-gum, an oil-type ointment, an emulsion-type ointment, a paste dentifrice, a powder dentifrice or a semi-paste dentifrice.

12. The method for treating or preventing periodontal diseases, in particular alveolar pyorrhea, which is characterised by applying to the gingivae superoxide dismutase or a composition as described in any one of the preceding claims.

13. The use of superoxide dismutase in the preparation of a composition for periodontal application.

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please quote
our reference FAC/MR/799P55423

your reference

date 3rd March 1988

Sir,

Re: Patent Application No. 873210331.1
in the name of MINORU NAKANO

We request that the following amendments be recorded in the file and that, if they are found otherwise allowable, we be given the opportunity to incorporate them on the pages of the Application at some convenient later date.

(a) Page 14, last line, add the omitted Example 8 reading as follows:-

"Example 8, immulsion-type ointment

An emulsion-type ointment is manufactured by a procedure analogous to that of Example 7, but with component A further including 0.01 g of catalase and with component B further inlcuding 1g of taurine."

(b) Page 7 line 14, please correct the spelling of "composition"

(c) Page 10, line 2 from below, please delete "loss" and insert "flail"

(d) Page 12 line 6, amend "5%" to "0.5%"

(e) Page 17 line 12, amend "10^{4}" to "10^{-4}"

Yours faithfully,
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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 273 579**
A3

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(21) Application number: 87310331.1

(51) Int. Cl.4: A61K 7/28 , A61K 37/24

(22) Date of filing: 23.11.87

(30) Priority: 22.11.86 JP 279497/86

(43) Date of publication of application:
06.07.88 Bulletin 88/27

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(88) Date of deferred publication of the search report:
10.05.89 Bulletin 89/19

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 31 0331

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A,P	WO-A-8 701 387 (SYN-TEK AB) * claims 60-65; page 9, line 4-5 *	1-13	A 61 K 7/28 A 61 K 37/50
A	PATENT ABSTRACTS OF JAPAN vol. 5, no. 85 (C-57) (757), 3rd June 1981; & JP - A - 56 32422 (MOCHIDA), 01-04-1981	1-13	
A	PATENT ABSTRACTS OF JAPAN vol. 5, no. 54 (C-50) (726), 15th April 1981; & JP - A - 56 7720 (MOCHIDA), 27-01-1981	1-13	
A	EP-A-0 070 656 (TAKEDA) * claims 7-9 *	1-13	
A	EP-A-0 045 222 (TAKEDA) * claims 5-6 *	1-13	
A	EP-A-0 172 577 (TAKEDA) * claims 3-4 *	1-13	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	LA RECHERCHE vol. 10, no. 106, December 1979, pages 1269 - 1270, Paris, FR; A.M. MICHELSON: "Une enzym qui nous veut du bien"	1-13	A 61 K A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	30-01-1989	AVEDIKIAN P.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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